

Detection and treatment of renovascular disease: 40 years on

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This year marks the 60th anniversary of the publication of Goldblatt's original demonstration that constricting the renal arteries of the dog was capable of causing sustained elevation of arterial pressure [1]. The success of those experiments depended not only on the ingenious design of the adjustable silver clamps which narrowed the arteries, but also on the ability to make accurate recordings of systolic blood pressure from day to day via external carotid loops. Translation from the laboratory to clinical practice was slow, and 20 years elapsed before Howard *et al.* [2] were able to show amelioration of hypertension after nephrectomy in a series of six patients in whom renovascular disease was suspected. That early series did not use angiography, which only later became established as the main technique for diagnosis.

Terminology

He thought he saw an Elephant
that practised on a fife;
he looked again and found it was
a letter from his wife

Sylvie and Bruno, Lewis Carroll

At least some of the problems of renovascular disease and hypertension in humans are semantic. The term 'renovascular hypertension', with its implication of causality, is often used loosely and sometimes interchangeably with the descriptive term 'renal artery stenosis'. The clinical literature often refers to 'cure' of hypertension in a sense that may be unrealistic when applied to some patients with atherosclerotic renal artery narrowing, who may

have structural changes in large arteries, impaired renal function and even pre-existing primary hypertension. Criteria for determining improvements in levels of arterial pressure after revascularization tend to be variable and poorly defined, and are often applied retrospectively. These are methods which would not be accepted for trials of antihypertensive drug treatment. Again, the importance or otherwise of changes in renal function after revascularization or medical treatment is not always well defined and there is a surprising dearth of well-designed clinical trials to inform decisions on best therapy.

The renin-angiotensin system

Experiment and debate have continued for more than 50 years on the role of renin and angiotensin in pathogenesis. In the early stages of hypertension due to a unilateral renal artery disease the role of increased renin secretion is firmly established, but there is uncertainty concerning the later stages and it appears that there is then an increasing role for sodium retention and expansion of extracellular fluid volumes due to reduced renal function.

Renovascular disease in humans is generally associated with activation of the renin-angiotensin system unless the disease is bilateral or associated with major impairment of renal function. Renovascular disease may exacerbate or precipitate cardiac failure in patients with compromised left ventricular function, and successful revascularization prompts an immediate natriuresis and diuresis [3]. In unilateral renal artery stenosis, extracellular fluid volumes measured by total exchangeable sodium tend to be reduced in patients with renovascular disease and activation of the renin system [4].

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Marked hyponatraemia and hypokalaemia with extreme activation of renin may develop when renovascular disease causes malignant hypertension, the so-called vicious circle which culminates in a re-emergence of renin secretion in the kidney contralateral to a unilateral arterial stenosis. It is not clear whether this further contribution to circulating renin is due to arteriolar lesions in the kidney or to overall depletion of body sodium. Patients with hyponatraemia and malignant hypertension are liable to excessive falls in arterial pressure after initiating antihypertensive treatment.

Prevalence

The prevalence of renovascular hypertension varies in a population, depending on the burden of atherosclerosis. If screening for renovascular hypertension is performed on unselected populations of antihypertensive patients, the overall prevalence seems to vary from approximately 1 to 4% [5,6] but rises with age [7]. The prevalence increases to 16% when patients selectively refer to centres specializing in renovascular hypertension are considered [8], and to 32% in some series of patients with malignant hypertension [5,6].

Atherosclerosis

Atherosclerosis is the cause of most renovascular disease, and is usually associated with disease of the abdominal aorta and often with symptomatic disease affecting the arteries to the legs. Lesions occur in the main renal arteries (uncommonly in branches) and sometimes affect one of two or multiple arteries. In advanced disease of the abdominal aorta plaque may cause ostial lesions of the renal arteries, which are difficult to treat. Stenosis of the renal arteries not infrequently progresses to occlusion, but another cause of sudden deterioration of kidney function is cholesterol embolism, usually caused by angiography or angioplasty. Arteritis of the Takayasu type is quite often a cause of renovascular disease in the Far East, and other rare causes are neurofibromatosis and blunt abdominal trauma.

Fibromuscular dysplasia

Most non-atheromatous renal artery lesions are due to renal artery dysplasia, which can be classified according to the predominant layer within the vessel wall that is affected: intimal, medial and adventitial forms of fibromuscular dysplasia have been described [9]. Of these, the medial type of fibrodysplasia occurs in about 70% of instances and is confined mostly to females (male:female ratio at least 1:5). The cause of the condition is not known, but several hypotheses have been advanced. The most important are:

1. The humoral hypothesis, which implicates oestrogens [9].

2. The genetic hypothesis, which is supported by familial occurrence. In a study of 20 families with fibromuscular dysplasia, one study [10] found evidence consistent with an autosomal dominant mode of inheritance with variable penetrance in 60% of cases.
3. The ischaemic hypothesis. Experimental occlusion of the nutritive vasa vasorum in dogs causes morphological changes of the vascular wall, which resemble fibromuscular dysplasia [11]. In some (but not all) studies there has been an excess prevalence of cigarette smoking in patients affected by the condition [12].

Because it is a rare condition, the prevalence of fibromuscular dysplasia in the population is not known. Even in a very selected group of hypertensives referred to the Mayo Clinic for investigation of high blood pressure, fibromuscular dysplasia was found in <2% and in 20–30% of patients with renovascular disease [9]. Similar arterial changes can also affect mesenteric, iliac and carotid arteries [13], and there is a significant incidence of spontaneous dissection leading to vascular occlusion. Dissection of the renal artery may present with flank pain, haematuria and hypertension, sometimes accompanied by fever.

Diagnosis and screening

Clinical pointers

Increasing age, impaired renal function and the presence of peripheral vascular disease are the main clinical pointers to renovascular disease. Severe systolic hypertension in an elderly patient is a quite common presentation of renovascular disease in the clinic.

Physical signs are not often helpful. Systolic-diastolic bruits lateral to the midline are heard only occasionally, and sometimes an abdominal aortic aneurysm is palpable. The presence of arterial disease elsewhere, especially in the legs, is a relatively good predictor of atheromatous renal artery stenosis. In patients undergoing routine angiography for investigation of peripheral vascular disease, up to 30% have angiographic evidence of unilateral renal artery stenosis and 10% have bilateral disease [14], although not all lesions are haemodynamically significant [15]. Another indicator of underlying renovascular disease is abnormal renal function, particularly if function worsens after treatment with an angiotensin converting enzyme (ACE) inhibitor [16]. Normalization of blood pressure after monotherapy with an ACE inhibitor in a patient with moderate-to-severe hypertension should also raise the question of renovascular disease, especially in cigarette smokers. Patients with hypertension in whom control deteriorates despite antihypertensive drug treat-

ment that does not include an ACE inhibitor should also be screened for renovascular disease. Hypokalaemia due to angiotensin-mediated stimulation of aldosterone is a well-recognized but uncommon presenting finding unless there is malignant hypertension with bilateral retinal haemorrhages.

Some North American investigators advocate measuring renin after a single dose of captopril as a screening test, giving sensitivity of 74% and specificity of 89% in their one series [17]. A somewhat lower specificity was found by Svetkey *et al.* [8] in a population with quite high prevalence. False-positive results tend to occur in a small subgroup of patients with essential hypertension who have raised plasma renin levels. Measurements of plasma renin without stimulation may also be used in untreated patients as a screening test, but most patients presenting with renovascular disease tend to be on treatment with antihypertensive drugs. Some patients have proteinuria, but most not exceeding 2 g/24 h: patients with severe hypertension occasionally have proteinuria in the nephrotic range, and particularly heavy proteinuria may signify arterial occlusion [18].

It is very doubtful whether screening for renovascular hypertension is cost-effective in most patients with mild-to-moderate hypertension. The positive predictive value of the available tests is low if the prevalence of renovascular hypertension is $\leq 5\%$. Clinicians need to be guided by the clinical index of suspicion. Ordinary renography using labelled hippuran, diethylenetriaminepentaacetic acid (DTPA), mercaptoacetyl triglycine (MAG3) or diatrizoate is not sufficiently sensitive or specific (both approximately 75%) to be used as a screening test but acute administration of ACE inhibitor greatly improves the diagnostic yield [19–22]. Current results in clinically selected patients show that a renogram after ACE inhibitor administration gives a diagnostic sensitivity up to 90% and specificity of almost 95% [19,21,22]. MAG3 is probably not as sensitive as DTPA. Some researchers have reported that hippuran renography after ACE inhibitor and with frusemide washout predicts the blood pressure response to revascularization with high sensitivity and specificity [22]. Taking the difference between renogram curves or glomerular filtration rates before and after ACE inhibitor seems to be very specific, but is probably insensitive [19]. Preliminary evidence suggests that hippuran renography after cyclo-oxygenase inhibition with high-dose aspirin (20 mg/kg) may also be useful in screening for renovascular disease [23]. Vasodilator prostanoids are important in maintaining renal plasma flow in kidneys with renal artery stenosis.

Direct imaging of the renal arteries using colour-coded duplex sonography has been claimed to be a good screening method [24], but satisfactory images cannot be obtained in one-quarter of patients,

and there are difficulties when multiple renal arteries are present. The technique can be applied to detect reduced pulsatility in interlobar arteries distal to stenosis, a method that shows more promise as a screening test [25] but depends on the skill of the operator.

Renal angiography remains the cornerstone of the investigation of renovascular disease. We and most others have abandoned the rapid-sequence intravenous urogram as a screening test, due to the low sensitivity and specificity and high dose of radiation [26]. Intravenous digital subtraction angiography allows visualization of the aorta and renal arteries in 90% of patients [8], but there may be poor definition of the origins of the renal arteries and very poor definition in patients with reduced cardiac output. Arteriography with fine-gauge catheters (3–5 French-gauge), digital subtraction imaging and a free-flush aortic injection of contrast is the method of choice to demonstrate renal artery stenosis; the procedure can often be carried out as a day case.

Measurement of renal vein renins has long been used in the investigation of suspected renovascular disease. Lateralization of renin secretion is often arbitrarily designated when the ratio of the renal vein renin on the side with the stenosis to the contralateral side is ≥ 1.5 [27,28]. In a prospective study using the results of angioplasty or reconstructive surgery as an end-point, the renal vein renin ratio has been shown to have low sensitivity (65%) and specificity (52%). There was also a significant occurrence of false-negative results and a poor correlation with blood pressure responses to intervention [29,30]. Unlike isotope renography, stimulation of renin secretion with an ACE inhibitor does not seem to enhance the diagnostic value of renal vein renin sampling [30]. Methods that depend on multiple simultaneous samples from each renal vein and a peripheral vein may improve the sensitivity, and there is preliminary evidence to suggest that the sensitivity is enhanced if the renin concentration rather than the renin activity is measured [31]. Confirmation of catheter position by measurements of venous oxygen tension or hippuran extraction might be a useful adjunct. In most instances measurement of renal vein renins is not helpful when there is bilateral disease, although sometimes the concentrations have been used as a guide in choosing the kidney for revascularization.

Phase-contrast magnetic resonance imaging shows some promise as a method of visualizing the renal arteries, but experience of this technique is still very limited.

Treatment

Strategies for treating renal arterial disease are not based on properly controlled trials and are mostly

informed by anecdotal experience based on a quite small series of patients treated at specialized centres. Early in the 1970s a retrospective comparison of groups of 100 patients treated medically and surgically reported lower mortality, risk of vascular events, incidence of azotaemia and better control of blood pressure in the surgical group [32], but those results should be viewed sceptically. In considering results of revascularization, atherosclerosis and fibromuscular disease need to be considered separately. For atherosclerosis particularly, the extent to which renal function should be used as a criterion to determine whether to attempt revascularization is not clear: an intention to improve function is most relevant in patients with bilateral disease. If there is severe stenosis upon angiography (>75%), between 12 and 40% of kidneys will develop arterial occlusion after 1 year [33–35]. In atherosclerotic renal artery disease, coexisting coronary artery disease or cerebrovascular disease are major factors that can limit life-expectancy. The widespread adoption of percutaneous angioplasty has extended revascularization treatment to patients considered unfit for surgery, but has made it even more difficult to choose the best treatment for patients who would previously have been treated surgically. In most centres the number of operations for renovascular disease in adults has declined greatly since the establishment of interventional radiology.

Percutaneous transluminal angioplasty

Angioplasty has been used increasingly for treatment, and results must be viewed against the background of an expansion in the size of the treated population compared with that treated surgically. True ostial lesions caused by encroachment of aortic plaques, which cannot be distinguished by angiography from very proximal lesions of the renal artery, respond poorly to angioplasty alone [36], probably because expansion and cracking of intima and media in the renal artery cannot readily achieve remodelling of the vessel. Because of the frequent occurrence of spasm or elastic recoil and low technical success rate (25% or less) these lesions are amenable to treatment with balloon-expandable stents [37,38]. Ostial lesions are often bilateral and associated with renal insufficiency, and treatment is then undertaken with the primary intention of improving function. Stents may also be used to improve technically poor angioplasties where arterial occlusion has occurred due to intimal flaps or thrombosis, and to treat primary occlusive events and arterial dissections. The use of anticoagulation for 3 months with warfarin to prevent restenosis after the procedure has not been determined. It is currently not clear whether the use of stents will improve the clinical results of angioplasty alone, described previously [39,40], but the immediate and short-term technical success rates are improved.

Concerning blood pressure control, Ramsay and Waller [40] performed a meta-analysis of results of angioplasty trials and concluded that for atherosclerotic lesions the benefits are disappointingly small (overall cure rate 24%). The effects on renal function in large series have not been well-described. The results of treating fibromuscular disease are better [40,41], but surgical revascularization and even nephrectomy in early years also gave good results in the same group. Distal extension of disease in the renal artery may still preclude angioplasty in fibromuscular dysplasia. The recurrence rate in fibromuscular disease has been estimated as approximately 10% after a follow-up period of up to 5 years [41]. Angioplasty of transplant renal artery stenosis compares very favourably with surgical correction [42], which is often technically difficult due to perivascular fibrosis.

For an experienced operator the immediate complication rate for angioplasty is approximately 5%. Heparin during the procedure and the use of large-gauge catheters quite often causes local haematoma [43]. Renal artery occlusion or rupture and cholesterol embolism may cause further impairment of renal function [39]. After 6 months or so restenosis due to myointimal hyperplasia may occur. In one series of more than 100 patients reviewed after an average of 9 months the incidence of restenosis was 16%, with higher rates in the presence of severe aortic atheroma [44]. There is evidence that angiotensin II may promote intimal proliferation in experimental animals [45], but there is no clinical evidence that its inhibition in humans affects the process and there are appreciable risks of provoking renal failure with ACE inhibitors in renovascular disease.

Surgery

With the widespread adoption of angioplasty it has become much more difficult to define the role of surgical revascularization in treatment. Nephrectomy is almost obsolete as a treatment of renovascular disease, except perhaps when a small non-functioning kidney has resulted from renal artery occlusion secondary to fibromuscular dysplasia. In fibromuscular disease good results are obtained with surgical revascularization [46,47] and extracorporeal branch artery reconstruction can allow treatment of disease that extends distally. Dysplasia in children tends to cause progressive vascular obstruction, so aorta–renal bypass with hypogastric artery or auto-transplantation are the preferred treatments.

Surgical treatment of renovascular disease has been comprehensively reviewed by Novick [48]. Operative mortality for the best surgeons is 5% or less, but this increases to 10–30% if the presence of aneurysm requires concurrent aortic replacement. Surgical revascularization may also improve renal function in some patients [49,50]. If kidney size is greatly reduced (<7.5 cm), then revascularization by

surgery or angioplasty is not often effective in restoring renal function: preoperative kidney biopsy to assess the extent of nephrosclerosis in such kidneys has fallen into disrepute. Surgery is seldom indicated for severe renal failure. However, in occasional instances of bilateral renal artery occlusion with collateral flow to a kidney of reasonable size (>8 cm) the effects of surgical revascularization on renal function have been dramatic [51]. Angioplasty and stenting is probably now the preferred approach in such patients, and may be attempted if renal size is preserved. Patients with atherosclerotic renal artery stenosis often have concurrent coronary artery disease and internal carotid stenosis [52], and preoperative evaluation of both should be considered. Renal failure caused by ACE inhibitors is usually reversible when treatment is stopped.

Medical treatment

In my view the hypertension associated with renal artery stenosis should be treated medically in the first instances.

High Blood Pressure, GW Pickering (1968)

Nearly 30 years on we are still unable to contradict Pickering's opinion with confidence. In confirmation of the importance of activation of the renin system in pathogenesis of hypertension due to unilateral renovascular disease, ACE inhibitors are often effective in lowering blood pressure [53], but adverse effects on glomerular filtration rate in kidneys affected by renovascular disease greatly limit their clinical usefulness. It has been suspected that this reduced glomerular filtration rate is caused by reduced glomerular filtration pressure as a consequence of afferent arteriolar vasodilation [54], but falls in arterial pressure themselves cause major declines in filtration in kidneys distal to an arterial stenosis, and the threshold for this effect is determined by the severity of the narrowing [55]. ACE inhibitor treatment can produce severe and life-threatening renal failure if renal artery stenosis is bilateral or occurs in a solitary kidney, and the risk is increased by concurrent treatment with loop diuretics [56]. The safety of long-term ACE inhibitor treatment in patients with unilateral renal artery stenosis or occlusion is not established and such patients are at risk of developing disease on the contralateral side. It has been suggested that renal artery occlusion may be more likely after ACE inhibitor treatment [57], but the evidence is anecdotal. The effects of treatment with angiotensin receptor antagonists and renin inhibitors have not been reported.

Renal function may also worsen if patients with renovascular disease are treated with potent cyclo-

oxygenase inhibitors, an adverse effect which is the basis of the recently developed aspirin renogram. Beta-adrenoceptor blockers inhibit renin secretion and are effective in treating renovascular hypertension, but it is sensible to monitor renal function. Calcium antagonists seem to be reasonably safe, but diuretics should be used with care, first because extracellular fluid volumes may already be reduced in unilateral renal artery stenosis, and secondly because of the interaction with ACE inhibitors leading to worsening renal failure in susceptible patients. Successful revascularization often improves hypertension and kidney function, but quite a high proportion of patients, most with atherosclerotic disease, still require long-term treatment with drugs.

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Notice of Multiple Publication

Two articles with substantially similar data have recently been published in the *Journal of Hypertension* and *Hypertension* [1,2]. Both articles were received simultaneously in the respective journal offices and describe a single experiment of varying salt intakes performed on a single study population of 163 white, non-obese non-hypertensive subjects. Both articles report and analyse data from this group, including body weight, mean arterial pressure, systolic and diastolic blood pressure, heart rate, metabolic data, and values for urinary sodium excretion and plasma renin activity. In addition, the article in the *Journal of Hypertension* reports the results for several measures of serum lipids. The *Hypertension* article includes reports of serum electrolytes. Both articles report division of the subjects into groups classified as salt-sensitive, salt-resistant and 'counter-regulators', with identical numbers reported in each group.

Aside from different sets of chemical values reported, and to some extent the focus of discussion sections of the two articles, the *Journal of Hypertension* also reports a subsequent experiment in a subset of 25 of the original group that was tested for blood pressure, plasma renin activity and serum lipid response to different salt regimens. This subsequent experiment was not discussed in the article in *Hypertension*.

This notice is being published simultaneously in both journals to emphasize two essential issues: first, both journal editors must be informed if authors wish to publish material from a single study by providing the alternative journal with a copy of the other manuscript; and secondly, there must be cross-referencing in both manuscripts as to the material included in the two papers.

The policy of our journals on multiple publication is clear. As stated in 'Instructions to Authors' we will publish only original material which has not appeared elsewhere in the literature and is not under review at the time of submission. If authors have any concerns, however remote, about multiple publication, they should raise these with the editors at the earliest possible opportunity.

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